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REVIEW

Galectin-1: a small protein with major functions

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Galectins are a family of carbohydrate-binding proteins with an affinity for β-galactosides. Galectin-1 (Gal-1) is differentially expressed by various normal and pathological tissues and appears to be functionally polyvalent, with a wide range of biological activity. The intracellular and extracellular activity of Gal-1 has been described. Evidence points to Gal-1 and its ligands as one of the master regulators of such immune responses as T-cell homeostasis and survival, T-cell immune disorders, inflammation and allergies as well as host–pathogen interactions. Gal-1 expression or overexpression in tumors and/or the tissue surrounding them must be considered as a sign of the malignant tumor progression that is often related to the long-range dissemination of tumoral cells (metastasis), to their dissemination into the surrounding normal tissue, and to tumor immune-escape. Gal-1 in its oxidized form plays a number of important roles in the regeneration of the central nervous system after injury. The targeted overexpression (or delivery) of Gal-1 should be considered as a method of choice for the treatment of some kinds of inflammation-related diseases, neurodegenerative pathologies and muscular dystrophies. In contrast, the targeted inhibition of Gal-1 expression is what should be developed for therapeutic applications against cancer progression. Gal-1 is thus a promising molecular target for the development of new and original therapeutic tools.

Key words: cancer/inflammation/neurodegeneration/ therapeutic application/tumor immune-escape

Galectins: an overview

Galectins are a phylogenetically conserved family of lectins defined in 1994 as a shared consensus of amino-acid-sequences of about 130 amino acids and the carbohydrate recognition domain (CRD) responsible for β-galactoside binding (Barondes *et al.*, 1994). Fifteen mammalian galectins have been identified to date. While some of these galectins contain one CRD and are biologically active as monomers (galectins-5, -7, -10), as homodimers (galectins-1, -2, -11, 13–14, -15) or as oligomers that aggregate though their non-lectin domain (galectin-3); others contain two CRDs connected by a short linker peptide (galectins-4, -6, -8, -9, -12). While the CRDs of all the galectins share an affinity for the minimum saccharide ligand *N*-acetyllactosamine—a common disaccharide found on many cellular glycoproteins—individual galectins can also recognize different modifications to this minimum saccharide ligand and so demonstrate the fine specificity of certain galectins for tissue- or developmentally-specific ligands (Ahmad *et al.*, 2004). Location studies of galectins have established that these proteins can segregate into multiple cell compartments in function of the status of the cells in question (Danguy *et al.*, 2002; Liu and Rabinovich, 2005). Although galectins as a whole do not have the signal sequence required for protein secretion through the usual secretory pathway, some galectins are secreted and are found in the extracellular space (Hughes, 1999). While the intracellular activity of galectin-1 (Gal-1) is mainly independent on its lectin activity, its extracellular activity is mainly dependent on it.

Gal-1: molecular structures at gene and protein levels

The first protein discovered in the family was Gal-1. As reported by the MapViewer program and the Entrez genome database on the NCBI website (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Genome&itool=toolbar), Gal-1 is encoded by the LSGALS1 gene located on chromosome 22q12 (Figure 1). The 0.6 kb transcript (GenBank: NM_002305) is the result of the splicing of four exons encoding a protein with 135 amino acids (GenPept : NP_002296, SwissProt: P09382) (Figure 2). Gal-1 occurs as a monomer as well as a non-covalent homodimer consisting of subunits of one CRD (Gal-1, ~29 kDa) (Barondes *et al.*, 1994; Cho and Cummings, 1995). Each form is associated with different biological activities, as detailed below.

The overall folding of Gal-1 involves a β sandwich consisting of two anti-parallel β-sheets (Figure 2). This jellyroll topology of the CRD constitutes the typical folding patterns of galectins. Human Gal-1 exists as a dimer in solution (Lopez-Lucendo *et al.*, 2004). The integrity of this dimer is maintained principally by interactions between the monomers at the interface and through the well-conserved hydrophobic core, a factor which explains the observed stability

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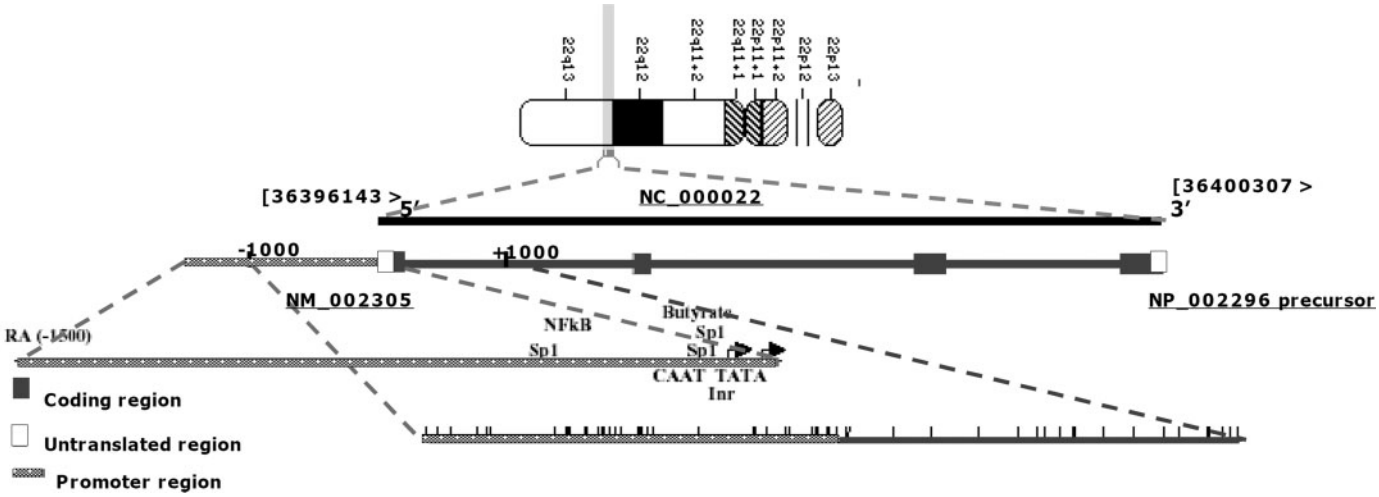

Fig. 1. Map of the Gal-1 gene on the human chromosome 22q12. The sequences were retrieved using the MapViewer program and the Entrez genome database on the NCBI website and were analyzed using the GeneWorks program produced by IntelliGenetics Inc. The curved arrows indicate the initial transcription start-up sites (Chiariotti *et al*., 2004). The 0.6 kb transcript results from the splicing of four exons (the boxes indicate the four coding regions) and encodes for a protein of 135 aminoacids.

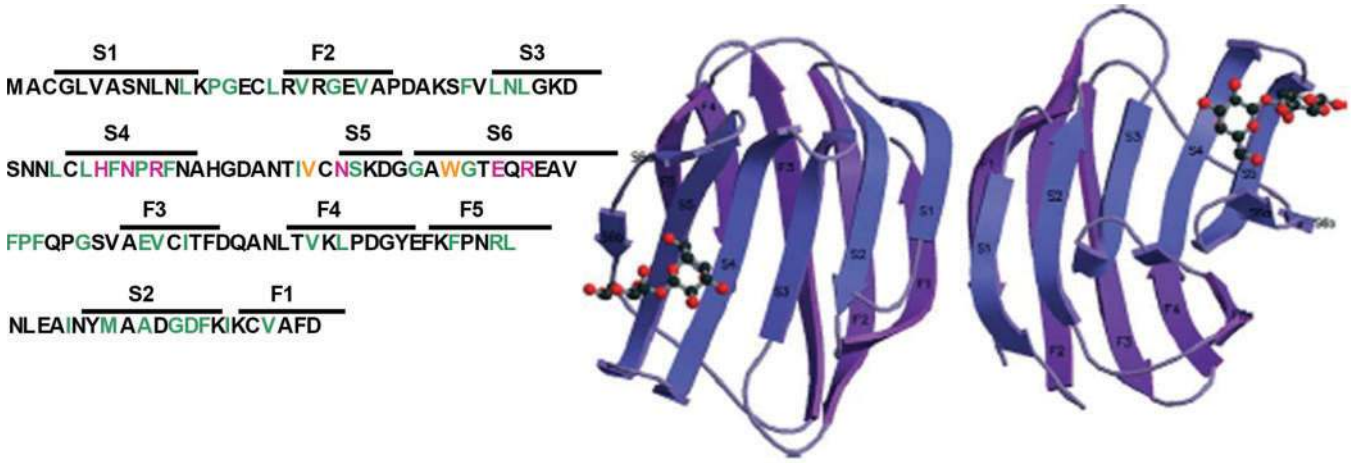

Fig. 2. Structure of Gal-1 protein. The overall folding of Gal-1 involves a β sandwich consisting of two anti-parallel β-sheets of five (F1–F5) and six (S1–S6a/b) strands respectively. The N and the C termini of each monomer are positioned at the dimer interface and the CRDs are located at the far ends of the same face, a configuration which constitutes a long, negatively charged cleft in the cavity (Lopez-Lucendo *et al*., 2004). The green amino acid symbols illustrate highly conserved residues. The key residues of the CRD, which is known to interact directly with bound carbohydrate by means of hydrogen bounds, are colored pink, while those interacting with carbohydrates via van der Waals interactions are orange (Cooper, 2002) and include His44, Asn46, Arg48, Val59, Asn61, Trp68, Glu71, and Arg73. The 3D ribbon diagram of the homodimeric human Gal-1 was designed with MOLSCRIPT by Lopez-Lucendo *et al*. (2004). A lactose (Galβ1–4Glc) is illustrated in the CRD.

of the dimer in molecular terms (Figure 2) (Lopez-Lucendo *et al*., 2004). Nevertheless, one of the main characteristics of the homodimeric Gal-1 protein is that it spontaneously dissociates at low concentrations (K_d ~ 7 μM) into a monomeric form that is still able to bind to carbohydrates (Cho and Cummings, 1995), but with a lower level of affinity (Leppanen *et al*., 2005). In the present paper Gal-1 will be used as the general term for both the monomeric and the dimeric product of the LGALS1 gene. We will clearly state monomeric (mGal-1) or dimeric galectin-1 (dGal-1) when reporting results specific to the monomer or the dimer form respectively. Gal-1 can also exist in an oxidized form, that is, a form that lacks lectin activity (Outenreath and Jones, 1992).

The regulation of Gal-1 expression

A small region spanning the initial transcription start-up site (–63/+45) is sufficient in the promoter region of the Gal-1 gene for its transcriptional activity in mice (Chiariotti *et al*., 2004) (Figure 1). Both an upstream and a downstream position-dependent *cis*-element are necessary for efficient transcriptional activity; an additional start-up site has been mapped at position-31, and an Sp1-binding site (–57/–48) and a consensus initiator (Inr) element (which partially overlaps a non-canonical TATA box) direct RNA initiation (Chiariotti *et al*., 2004) (Figure 1). The upstream transcripts contribute to more than half of the Gal-1 mRNA population (Figure 1). The 5′- end of this transcript

Table I. The regulation of Gal-1 expression

Effectors	Types	Doses	Tissues	Effects	References
5-Azacytidine	Demethylation of promoter	–	Hepatocellular carcinomas (hu), liver, thyroid cells (rat), osteosarcoma cells (hu)	↑	Kondoh *et al.*, 2003; Chiariotti *et al.*, 2004
	Irreversible promoter demethylation	2 μM	T leukemia cells (hu)	↑	Poirier *et al.*, 2001; Chiariotti *et al.*, 2004
		10 μM	B lymphomas (hu)	↑	
Benzodiazepine	Peripheral benzodiazepine receptor	–	Jurkat T lymphoma cells (hu)	↓	Rochard *et al.*, 2004
Budesonide glucocorticoid	Anti-inflammatory	250 ng/mL	Nasal polyps (hu)	↑	Delbrouck *et al.*, 2002
Cyclophosphamide	Antimetastatic alkylating drug	Low dose, 10 mg/kg	Lymphomas (rat)	↓	Rabinovich, Rubinstein *et al.*, 2002
ERBB2 overexpression	HER2/neu oncogene		Breast cancer cells (hu)	↑	Mackay *et al.*, 2003
Hepatitis C virus core protein/ethanol	MAPK (ERK/p38) activation	–	Liver (mo)	↑	Tsutsumi *et al.*, 2003
Imp (–/–) mice	Insulin-like growth factor II mrRNA-binding protein 1 (IMP1)	–	Impaired gut development (mo)	↓	Hansen *et al.*, 2004
Minimally oxidized low-density lipoprotein (MM-LDL)	Pro(?)-inflammatory circulating lipoprotein	100 μg/mL	Endothelial cells (hu)	↑	Baum *et al.*, 1995; Perillo *et al.*, 1995
Progesterone	Hormones	Receptor antagonist blocks gal-1 expression	Uterine tissue (mo)	↑	Choe *et al.*, 1997
Estrogen			Uterine tissue (mo)	↑	Choe *et al.*, 1997
Estrogen/delta fosB			Rat1a embryo cells (rat)	↑	Tahara *et al.*, 2003
Thyroid stimulating hormone (TSH)		1 nM	Thyroid (rat)	↑	Chiariotti *et al.*, 1994
Retinoic acid (all-trans)	Differentiating	1 μM	Embryonal carcinomas, myoblastic cells (mo)	↑	Lu *et al.*, 2000
		–	Transformed neural cells (rat)	↓	Chiariotti *et al.*, 1994
			Cholesteatomas (hu)	Relation with level of receptor expression	Simon *et al.*, 2001
Sodium butyrate	Differentiating	1–4 mM	Colon carcinomas (hu)	↑	Ohannesian *et al.*, 1994
		3 mM	HNSCCs (hu)	↑	Gillenwater *et al.*, 1998
		–	Embryonal carcinomas (mo)	↑	Lu and Lotan, 1999
		2–5 mM	Globelet cells (hu)	↑	Gaudier *et al.*, 2004
		2.5–10 mM	Prostate cancers (hu)	↑	Ellerhorst, Nguyen, Cooper, Estrov *et al.*, 1999
Valproic acid	Antiepileptic drug, inducer of neural tube defects		Embryo (mo)	↑	Kultima *et al.*, 2004

Hu, human; mo, mouse; ↓, decreases and/or inhibits; ↑, increases and/or favors; ?, uncertain.

is extremely GC-rich and may fold into a stable hairpin structure which could influence translation (Chiariotti *et al.*, 2004). The approximate position of the other putative and/or characterized regulatory elements is indicated in Figure 1 and relates to the CAAT box, to the nuclear factor kappaB-binding site (NF-κB) and to the sodium butyrate and retinoic acid (RA) response sequences. The various physicochemical agents already known as being able to modulate the expression of Gal-1 are listed in Table I. The methylation status of the Gal-1 promoter is also a very important mechanism that controls the expression of the gene (Chiariotti *et al.*, 2004).

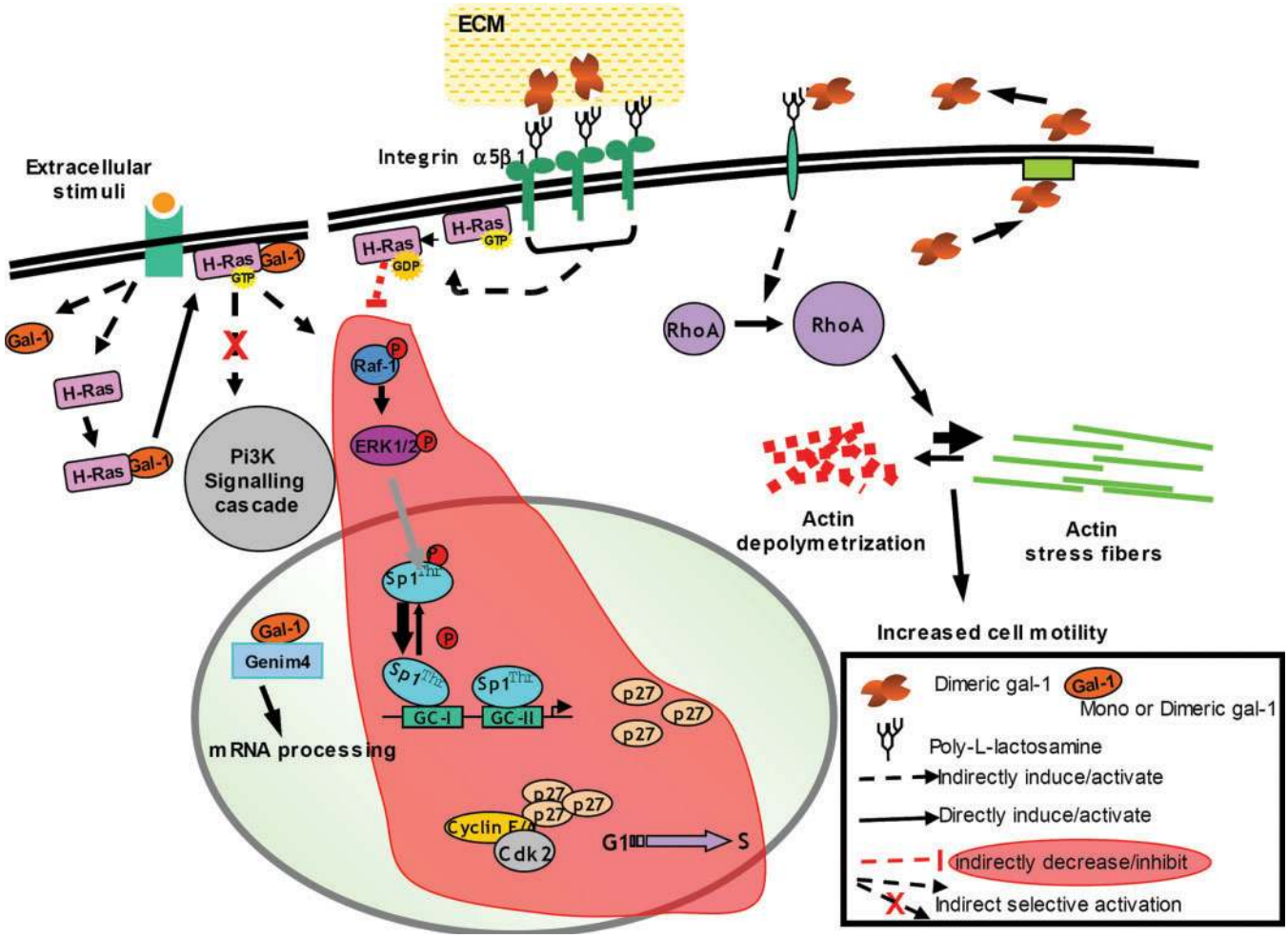

Fig. 3. Gal-1 and cell signaling. Gal-1 is present both inside and outside cells, and has both intracellular and extracellular functions. The extracellular functions require the carbohydrate-binding properties of dGal-1 while the intracellular ones are associated with carbohydrate-independent interactions between Gal-1 and other proteins. The Gal-1 induced growth inhibition requires functional interactions with the α5β1 integrin (Fischer *et al*., 2005). The antiproliferative effects result from the inhibition of the Ras-MEK-ERK pathway and the consecutive transcriptional induction of p27: two Sp1-binding sites in the p27 promoter are crucial to Gal-1 responsiveness (Fischer *et al*., 2005). The inhibition of the Ras-MEK-ERK cascade by Gal-1 increases Sp1 transactivation, with DNA binding relating to the reduced threonine-phosphorylation of Sp1 (Fischer *et al*., 2005). Furthermore, Gal-1 induces p21 transcription and selectively increases p27 protein stability. The Gal-1-mediated accumulation of p27 and p21 inhibits Cdk2 activity and, ultimately, results in G1 cell cycle arrest and growth inhibition (Fischer *et al*., 2005). The Gal-1-induced increase in cell motility involves the Gal-1-induced increase in rhoA expression and the alteration of the polymerization of the actin cytoskeleton (Camby *et al*., 2002). Gal-1 is recruited from the cytosol to the cell membrane by H-Ras-GTP in a lactose-independent manner with the resulting stabilization of the H-Ras-GTP, the clustering of the H-RAS-GTP and Gal-1 in non-raft microdomains (Prior *et al*., 2003), the subsequent binding to Raf-1 (but not to PI3Kinase) and the activation of the ERK signaling pathway (Elad-Sfadia *et al*., 2002). Nuclear Gal-1 interacts with Gemin4 and is co-immunoprecipitated with the nuclear SMN complexes involved in the splicing pathway (Vyakarnam *et al*., 1997).

The subcellular distribution and the export of Gal-1

Gal-1 is present both inside and outside cells and has both intracellular and extracellular functions (Figure 3). Gal-1 shows the characteristics of typical cytoplasmic proteins as well as an acetylated N-terminus and a lack of glycosylations (Clerch *et al*., 1988) (Figure 2); it has been described in cell nuclei and cytosols and also translocates to the intracellular side of cell membranes (Figure 3). Nevertheless, even though Gal-1 lacks recognizable secretion signal sequences and does not pass along the standard endoplasmic reticulum/Golgi pathway (Hughes, 1999), it is well-known that it is secreted and can be found on the extracellular side of all cell membranes as well as in the extracellular matrices of various normal and neoplastic tissues (Cooper and Barondes, 1990; van den Brule *et al*., 1997, 2003; Clausse *et al*., 1999; Camby *et al*., 2002; Danguy *et al*., 2002; von Wolff *et al*., 2005). There is evidence that this protein is secreted in a manner similar to fibroblast growth factor-2 (FGF-2) (Nickel, 2005) via inside-out transportation involving direct translocation across the plasma membrane of mammalian cells and requiring as yet unidentified integral membrane proteins and cytosolic factors (Nickel, 2005). The β-galactoside-binding site may constitute the primary targeting motif for galectin export machinery using β-galactoside-containing surface molecules as export receptors for intracellular Gal-1

(Nickel, 2005). As a consequence there is a quality control mechanism present since the export machinery recognizes only properly folded Gal-1. The similarity of the FGF-2 and Gal-1 export pathways suggests an important role for the sodium pump (the Na^+/K^+–ATPase) in their export features because ouabain, a selective inhibitor of the sodium pump, inhibits these export processes (Nickel, 2005).

Gal-1 binding partners

Although galectins in general, and Gal-1 in particular, were first described as lectins that bind β-galactosides, it is now clear from the literature that as well as being a lectin, Gal-1 is also engaged in protein–protein interactions (Table II). Interestingly enough, in most cases the lectin activity of Gal-1 is observed when it is extracellular, while the protein–protein interactions of Gal-1 concern its intracellular functions. The fact nevertheless remains that one can wonder what is the real biological relevance of such a high number of Gal-1 binding partners (Table II). Binding affinity studies are warranted in order to determine the potential binding partners which are real for Gal-1 and the ones which are not because they are associated with excessively weak affinities.

Protein–carbohydrate partnering

The lectin activity of Gal-1 relates to its carbohydrate-binding site (Figure 2). Sugar binding is enthalpically driven, and this supports the notion that van der Waals contacts and hydrogen bonds constitute the main forces driving and/or stabilizing complex formations (Lopez-Lucendo *et al.*, 2004). The published dissociation constant of dGal-1 with various glycoproteins is about 5 μM (Symons *et al.*, 2000). Although dGal-1 binds preferentially to glycoconjugates containing the ubiquitous disaccharide *N*-acetyllactosamine (Gal-β1–3/4 GlcNAc also known as LacNAcII or type 2 saccharide), its binding to individual lactosamine units is characterized by relatively low levels of affinity (K_d ~ 50 μM) (Schwarz *et al.*, 1998; Ahmad *et al.*, 2004). It is the arrangement of lactosamine disaccharides in multiantennary repeating chains (up to three branches) that increases the binding avidity (K_d ~ 4 μM) (Schwarz *et al.*, 1998; Ahmad *et al.*, 2004). In contrast, there is no increase in avidity when the recognition unit is repeated in a string (poly-*N*-lactosamine) (Ahmad *et al.*, 2004). In polysaccharides, dGal-1 does not bind glycans that lack a terminal non-reducing unmodified *N*-acetyllactosamine (Di Virgilio *et al.*, 1999; Stowell *et al.*, 2004). Although terminal galactose residues are important for dGal-1 recognition, dGal-1 binds similarly to α3-sialylated (created by ST3Gal III sialyltransferase) and α2-fucosylated (created by fucosyltransferase) terminal *N*-acetyllactosamine, but not to α6-sialylated or α3-fucosylated terminal *N*-acetyllactosamine (Amano *et al.*, 2003; Leppanen *et al.*, 2005). Whether extended or otherwise, free ligands in solution bind dGal-1 with a relatively low level of affinity (Leppanen *et al.*, 2005); in contrast, the avidity of dGal-1 for extended glycans is enhanced when it is surface-bound as on cell surfaces or in extracellular matrix (ECM) (He and Baum, 2004).

In the ECM. Gal-1 binds to a number of ECM components in a dose-dependent and β-galactoside-dependent manner in the following order: laminin > cellular fibronectin > thrombospondin > plasma fibronectin > vitronectin > osteopontin (Moiseeva *et al.*, 2000; Moiseeva, Williams, and Samani, 2003). Laminin and cellular fibronectin are glycoproteins which are highly N-glycosylated with bi- and tetra-antennary poly-*N*-lactosamines (Carsons *et al.*, 1987; Fujiwara *et al.*, 1988). Gal-1 is also involved in ECM assembly and remodeling: it inhibits the incorporation of vitronectin and chondroitin sulphate B into the ECM of vascular smooth muscle cells (Moiseeva, Williams, and Samani, 2003). The interaction of Gal-1 with vitronectin seems to depend on vitronectin conformation since it preferentially recognizes unfolded vitronectin multimers rather than inactive folded monomers (Moiseeva, Williams, and Samani, 2003).

Cell surface-binding partners. Various membrane glycoproteins have been identified as the binding partners of Gal-1 for the mediation of cell–cell or cell–ECM adhesion (Table II). We detail below some of the major cell surface-binding partners of Gal-1.

Integrins. The activity of integrin adhesion receptors is essential for normal cellular function and survival (Frisch and Ruoslahti, 1997; Stupack and Cheresch, 2002). N-glycosylations of β-integrins regulate β1 integrin functions by modulating their heterodimerization with α chains and ligand-binding activity (Gu and Taniguchi, 2004). Numerous variants of integrin glycoforms have been described in many normal and pathological cell types. Via its direct binding to β1 integrins (without cross-linking them) dGal-1 increases the amounts of partly activated β1 integrins, but does not induce dimerization with α subunits (Moiseeva, Williams, and Samani, 2003). In the case of vascular smooth muscle cells this interaction of Gal-1 with the α1β1 integrin has been reported both as transiently phosphorylating the focal adhesion kinase (FAK) and as modulating the attachment of cells and their spreading and migration on laminin, but not on cellular fibronectin (Moiseeva *et al.*, 1999; Moiseeva, Williams, and Samani, 2003). Gal-1 is secreted during skeletal muscle differentiation and accumulates with laminin in the basement membrane surrounding each myofiber (Gu *et al.*, 1994). The coincidence of Gal-1 secretion with the onset of myoblast differentiation and fusion and the transition in myoblast adhesion and mobility on laminin are regulated by the interaction of Gal-1 with laminin and the α7β1 integrin (Gu *et al.*, 1994). As a consequence Gal-1 inhibits the association of the α7β1 integrin with laminin, and is thus able to prevent and dissociate the interaction of cells with laminin in a dose-dependent fashion (Gu *et al.*, 1994). In contrast, Gal-1 does not affect the binding of cells on fibronectin via the same α7β1 integrin (Gu *et al.*, 1994). Fischer *et al.* (2005) have recently shown on a panel of epithelial cell carcinomas that Gal-1-induced growth inhibition requires functional interactions with the α5β1 integrin.

As far as other integrins are concerned, Gal-1 from mouse macrophages has been found to specifically associate with the $\alpha_M\beta2$ integrin (the complement receptor 3, CR3) (Avni *et al.*, 1998).

Table II. The binding partners of Gal-1

Binding partners	Monomeric/ dimeric Gal-1	Binding type (P–C, P–P)	Cell/tissue types	Biological functions	References
β1 integrin	Dimeric				
α1β1, α7β1		P–C	Skeletal and vascular SMC	Adhesion, FAK activation	Gu *et al.*, 1994; Moiseeva *et al.*, 1999; Moiseeva, Williams, Goodall *et al.*, 2003
α5β1		P–C	Epithelial carcinoma cells	Inhibit ras-MEK-ERK pathway, increase p21 and p27, and growth inhibition	Fischer *et al.*, 2005
$\alpha_M\beta2$ integrin		P–C	Macrophage, neutrophils (?)	NS activation	Avni *et al.*, 1998; Almkvist *et al.*, 2002
1B2 glycolipid	NS	P–C	Olfactory axon in olfactory bulb	↑ cell–cell and cell–laminin adhesion	Mahanthappa *et al.*, 1994
Actin	NS	P–P	Brain	NS	Joubert *et al.*, 1992
		P–C (?)	MOLT-4 T cells		Pace *et al.*, 1999
CA-125	NS	P–C	HeLa cells	Gal-1 export (?)	Seelenmeyer *et al.*, 2003
CD2/CD3	Dimeric	P–C	Jurkat T cells	Membrane redistribution, induction of cell death	Pace *et al.*, 1999; Walzel *et al.*, 2000
CD4	Dimeric	P–C	T cell	NS	Pace *et al.*, 1999; 2000
CD43	Dimeric	P–C	T cells	Membrane redistribution, induction of cell death	Pace *et al.*, 1999; Nguyen *et al.*, 2001; Lanteri *et al.*, 2003
CD45	Dimeric	P–C	T, B cells	Membrane redistribution, induction of cell death	Perillo *et al.*, 1995; Fouillit *et al.*, 2000; Symons *et al.*, 2000; Fajka-Boja *et al.*, 2002
CD7	NS	P–C	T cells	Induction of cell death	Pace *et al.*, 1999, 2000
Carcino embryonic antigen (CEA, CD66e)	NS	P–C	KM12 colon carcinoma cells	NS	Ohannesian *et al.*, 1994
Cytochrome oxidase subunit III	NS	P–P (?)	HeLa cells	NS	Park *et al.*, 2001
Fibronectin	NS	P–C	Ovarian carcinoma, placenta	↑ adhesion	Ozeki *et al.*, 1995; Moiseeva *et al.*, 2000; Moiseeva, Williams, and Samani, 2003; van den Brule *et al.*, 2003
Genim-4 nuclear and (?) cytoplasmic	NS	P–P	HeLa cells	preRNA splicing, RNA interference	Park *et al.*, 2001; Hutvagner and Zamore, 2002
Glycoprotein 90K (MAC-2BP)	NS	P–C	A375 melanoma cells	↑ cell aggregation	Tinari *et al.*, 2001
Glycosaminoglycan (chondroitin sulphate B, heparan sulfate)	NS	P–C	VSMC	Modulation of ECM assembly, ↓ adhesion	Moiseeva, Williams, Goodall *et al.*, 2003
GM1 ganglioside	Dimeric	P–C	SK-N-MC neurobastoma cells	↓ growth	Kopitz *et al.*, 1998, 2001; Andre *et al.*, 2004
HBGp82	NS	P–C	Brain	NS	Chadli *et al.*, 1997
H-ras	Dimeric	P–P	HeLa, HEK293, Rat-1, 293T cells	↑ ras activation with selective activation of Raf-1/ERK pathway	Paz *et al.*, 2001; Elad-Sfadia *et al.*, 2002; Prior *et al.*, 2003; Rotblat *et al.*, 2004
Laminin	NS	P–C	Melanomas, myoblasts, ovarian carcinomas, Leydig cells, placenta	↑ adhesion	Ozeki *et al.*, 1995; Moiseeva *et al.*, 2000; Moiseeva, Williams, Goodall *et al.*, 2003; van den Brule *et al.*, 2003; Martinez *et al.*, 2004
LAMP-1 (CD107a), LAMP-2 (CD107b)	NS	P–C	Ovarian, colon carcinomas	↑ adhesion	Ohannesian *et al.*, 1994; Woynarowska *et al.*, 1994
Mucin	NS	P–C	Epithelial glycocalyces of gastric and intestinal mucosa	NS	Wasano and Hirakawa, 1997

Table II. continued

Binding partners	Monomeric/ dimeric Gal-1	Binding type (P–C, P–P)	Cell/tissue types	Biological functions	References
Osteospontin	NS	P–C	VSMC	↑ adhesion	Moiseeva *et al.*, 2000
Pre-B cell receptor	NS	P–C	B cell lines	↑ adhesion, cell diffrentiation	Gauthier *et al.*, 2002
SUMO-3/SMT3B	NS	P–P (?)	HeLa cells	NS	Park *et al.*, 2001
Thrombospondin	NS	P–C	VSMC	↑ adhesion	Moiseeva *et al.*, 2000
Thy-1	NS	P–C	T cells	NS	Symons *et al.*, 2000
Vitronectin	NS	P–C	VSMC	ECM assembly	Moiseeva, Williams, and Samani, 2003

FAK, facal adhesion kinase; P–C, protein–carbohydrate interaction; P–P, protein–protein interaction; NS, not specified; VSMC, vascular smooth muscle cell; ↓, decreases and/or inhibits; ↑, increases and/or favors; ?, uncertain.

CD2, CD3, CD7 CD43, CD45. A number of T-cell glycoproteins from MOLT-4 and Jurkat human T cells have been shown to be specific receptors for mammalian Gal-1 binding: CD45, CD43, CD7 (Pace *et al.*, 1999; Walzel *et al.*, 1999; Symons *et al.*, 2000; Fajka-Boja *et al.*, 2002). The functions of these receptors are detailed further in the review.

GM1 ganglioside. Gal-1 is a major receptor for the carbohydrate portion of the ganglioside GM1 exposed on the surface of human neuroblastoma cells (Kopitz *et al.*, 1998; Andre *et al.*, 2004). Cell confluence increases the surface presentation of dGal-1. Under these circumstances Gal-1 acts as a negative growth regulator of neuroblastoma cells, though without being pro-apoptotic (Kopitz *et al.*, 1998, 2001).

Protein–protein partnering

The proteins identified so far that interact in a carbohydrate-independent manner with Gal-1 are not structurally related to each other and do not seem to share any common domains or motifs (Table II). The galectin sites that are involved in these interactions have not yet been established.

Gemin4. Gemin4 is found in the cytoplasm as well as in the nucleus of cells both as a member of the survival of motor neuron protein (SMN) complex and as the miRNP particle (microRNA [MiRNA] ribonucleoprotein [RNP]). The cytoplasmic SMN complex plays a role in the biogenesis of snRNPs in the cytoplasm before their entry into the nucleus (Paushkin *et al.*, 2002). Nuclear SMN-containing complexes are thought to recycle and/or resupply snRNPs to the early (H/E) complexes in the spliceosome assembly pathway and so to be involved in the processes that direct pre-mRNA splicing (Paushkin *et al.*, 2002). Thus, the findings that nuclear Gal-1 interacts with Gemin4 and is co-immunoprecipitated with nuclear SMN complexes (Park *et al.*, 2001) offer mechanistic insights into its potential role in the splicing pathway (Vyakarnam *et al.*, 1997) by involving the H/E complex as the locus of action of Gal-1 in the spliceosome assembly (Figure 3).

Ras. Gal-1 interacts in a lactose-independent manner with H-Ras-guanosine triphosphate (H-Ras-GTP) through its farnesyl cystein carboxymethylester (Paz *et al.*, 2001; Rotblat *et al.*, 2004) and so strengthens its membrane association (Paz *et al.*, 2001). The binding of Gal-1 to Ras is one of the most interesting and potentially significant functions of Gal-1. We will therefore detail these functions in the following section.

The effect of Gal-1 on cell signaling pathways

Regulation of cell growth

While extracellular Gal-1 has no effect on the growth rates of naïve T cells (Endharti *et al.*, 2005) or of astrocytic (Camby *et al.*, 2002) or colon (Hittelet *et al.*, 2003) tumor cell lines, Gal-1 is mitogenic for various types of normal or pathological murine and human cells, that is, murine Thy-1-negative spleen or lymph node cells (Symons *et al.*, 2000), mammalian vascular cells (Sanford and Harris-Hooker, 1990; Moiseeva *et al.*, 2000), and hepatic stellate cells (Maeda *et al.*, 2003). Gal-1 inhibits the growth of other cell types such as neuroblastoma (Kopitz *et al.*, 2001) and stromal bone marrow cells (Andersen *et al.*, 2003). Interestingly enough, it has been reported that depending on the dose involved, Gal-1 causes the biphasic modulation of cell growth. While high doses (~1 μM) of recombinant Gal-1 inhibit cell proliferation independently of Gal-1 sugar-binding activity, low doses (~1 nM) of Gal-1 are mitogenic and are susceptible to inhibition by lactose (Adams *et al.*, 1996; Vas *et al.*, 2005). While the knock-down of Gal-1 expression in murine melanomas (Rubinstein, Alvarez *et al.*, 2004) and human glioma cells (our unpublished data) does not affect their growth rate *in vitro,* it does decrease it in 9L rat gliosarcomas (Yamaoka *et al.*, 2000). Furthermore, Gal-1 can also regulate cell cycle progression in human mammary tumor cells (Wells *et al.*, 1999). The seemingly paradoxical positive and negative effects of Gal-1 on cell growth are highly dependent on cell type and cell activation status, and might also be influenced by the relative distribution of monomeric versus dimeric, or intracellular versus extracellular, forms.

Regulation of Cell Migration Processes

While cell migration is the net result of adhesion, motility, and invasion (Lefranc *et al.*, 2005; Decaestecker *et al.*, forthcoming),

Gal-1 modifies each of these three cell migration-related processes.

Adhesion. Gal-1 has been shown to increase the adhesion of various normal and cancer cells to the ECM via the cross-linking of glycoproteins (integrins) exposed on the cell surfaces with carbohydrate moieties of ECM components such as laminin and fibronectin (Ellerhorst, Nguyen, Cooper, Lotan *et al*., 1999; Moiseeva *et al*., 1999; van den Brule *et al*., 2003). In addition, Gal-1 can also mediate homotypical cell interaction, so favoring the aggregation of human melanoma cells (Tinari *et al*., 2001) and heterotypical cell interactions such as the interaction between cancer and endothelial cells, which, in its turn, favors the dispersion of tumor cells (Clausse *et al*., 1999; Glinsky *et al*., 2000).

Motility. Gal-1 causes the increased motility of glioma cells and the reorganization of the actin cytoskeleton associated with an increased expression of RhoA, a protein that modulates actin polymerization and depolymerization (Camby *et al*., 2002) (Figure 3). Conversely, the knockdown of Gal-1 expression in glioma cells reduces motility and adhesiveness (Camby *et al*., 2002, 2005). Oxidized Gal-1 (see *Gal-1 in pathological nervous systems*) stimulates the migration of Schwann cells from both the proximal and the distal stumps of transected nerves and promotes axonal regeneration after peripheral nerve injury (Fukaya *et al*., 2003). In colon carcinomas a Gal-1-enriched ECM decreases colon carcinoma cell motility (Hittelet *et al*., 2003).

Invasion. Using a proteomic approach based on the comparison of highly and poorly invasive mammary carcinoma cell lines, Harvey *et al*. (2001) identified the membrane expression of Gal-1 as a signature of cell invasiveness.

Interaction between Gal-1 and Ras

Ras genes which are frequently mutated in human tumors promote malignant transformation (Paz *et al*., 2001). Ras transformation requires membrane anchorage, which is promoted by Ras farnesylcysteine carboxymethylester and a second signal. The overexpression of Gal-1 increases membrane-associated Ras, Ras-GTP, and active ERK results in cell transformations, which are blocked by dominant negative Ras (Paz *et al*., 2001). Gal-1 antisense RNA inhibits transformations by H-Ras and abolishes the membrane anchorage of green fluorescent protein (GFP)-H-Ras, but not of GFP-H-Ras wild-type, GFP-K-Ras, and GFP-N-Ras (Paz *et al*., 2001). Thus, H-Ras–Gal-1 interactions establish an essential link between two proteins associated with cell transformation and human malignancies that can be exploited to selectively target oncogenic Ras proteins. In fact, H-Ras-GTP recruits Gal-1 from the cytosol to the cell membrane with the resulting stabilization of H-Ras-GTP, the clustering of H-Ras-GTP and Gal-1 in non-raft microdomains (Prior *et al*., 2003), the subsequent binding to Raf-1 (but not to PI3Kinase), the activation of the ERK signaling pathway and, finally, increased cell transformation (Elad-Sfadia *et al*., 2002) (Figure 3). So, in addition to increasing and prolonging H-Ras activation, the Gal-1-H-Ras complex renders the activated molecule selective toward Raf-1, but not toward PI3K (Ashery *et al*., forthcoming) (Figure 3). Fischer *et al*. (2005) have observed that the antiproliferative potential of Gal-1 in a number of carcinoma cell lines requires functional interaction with the $\alpha5\beta1$ integrin. Antiproliferative effects result from the inhibition of the Ras-MEK-ERK pathway and the consecutive transcriptional induction of p27, whose promoter contains two Sp1-binding sites crucial for Gal-1 responsiveness (Fischer *et al*., 2005). The inhibition of the Ras-MEK-ERK cascade by Gal-1 increases Sp1 transactivation and DNA binding due to the reduced threonine phosphorylation of Sp1. In addition, Gal-1 induces p21 transcription and selectively increases p27 protein stability, while the Gal-1-mediated accumulation of p27 and p21 inhibits cyclin-dependent kinase 2 activity, a process which ultimately results in G1 cell cycle arrest and growth inhibition (Fischer *et al*., 2005).

Rotblat *et al*. (2004) have identified a hydrophobic pocket in Gal-1 analogous to the Cdc42 geranylgeranyl-binding cavity in RhoGDI. This pocket possesses homologous isoprenoid-binding residues including the critical L11, whose RhoGDI L77 homologue changes dramatically on Cdc42 binding. By substituting L11A, Rotblat *et al*. (2004) obtained a dominant interfering Gal-1 that possesses a normal carbohydrate-binding ability but inhibits H-Ras GTP-loading and extracellular signal-regulated kinase activation, dislodges H-Ras from the cell membrane and attenuates H-Ras fibroblast transformation and PC12-cell neurite outgrowth. Thus, whereas Gal-1 cooperates with Ras independently of carbohydrate binding, Gal-1 (L11A) inhibits it.

Gal-1 in embryonic and adult tissue development and differentiation

Menstrual cycle, early gestation and embryogenesis

Gal-1 expression has been reported in male and female gonads (Wollina *et al*., 1999; Timmons *et al*., 2002; Dettin *et al*., 2003), and exogenously added Gal-1 has an inhibitory effect both on the steroidogenic activity of Leydig cells in the testicles (Martinez *et al*., 2004) and on the granulosa cells in the ovary (Jeschke *et al*., 2004; Walzel *et al*., 2004).

In the uterus Gal-1 expression is restricted to the endometrium (Maquoi *et al*., 1997) and varies during the menstrual cycle and the early phases of gestation (von Wolff *et al*., 2005). The expression of Gal-1 increases significantly in the late secretory phase endometrium and in decidual tissue (Maquoi *et al*., 1997; von Wolff *et al*., 2005), and shows a specific pattern of expression in trophoblastic tissue (Maquoi *et al*., 1997; Vicovac *et al*., 1998).

During the first trimester of human embryogenesis Gal-1 is expressed in connective tissue, in smooth and striated muscles, and in some epithelia such as the skin, the gonads, the thyroid gland, and the kidneys (van den Brule *et al*., 1997; Savin *et al*., 2003; Hughes, 2004; von Wolff *et al*., 2005).

Differentiation of the myogenic lineage

During the course of myoblast differentiation intracellular Gal-1 is externalized as myoblasts fused into myotubes (Cooper and Barondes, 1990). The role of Gal-1 in the case of myoblast fusion may be explained by the fact that the

adherence of the myoblast to the extracellular component laminin is disrupted in the presence of Gal-1 (Cooper *et al.*, 1991) via the selective modulation by Gal-1 of the interaction between the α7β1 integrin and fibronectin and laminin (Gu *et al.*, 1994). Although the exact role of Gal-1 in myogenesis remains to be seen, this galectin has been shown to induce non-committed myogenic cells in the dermis to express myogenic markers. It increases the terminal differentiation of committed myogenic cells and has a role to play in the development and regenerative ability of muscles (Cooper and Barondes, 1990; Cooper *et al.*, 1991; Harrison and Wilson, 1992; Goldring *et al.*, 2002). Gal-1 may thus be regarded as a potentially important tool in the treatment of cases of human muscular dystrophy (Goldring *et al.*, 2002).

Differentiation of the hematopoietic lineage

Mesenchymal cells give rise to the stromal marrow environment that supports hematopoiesis. These cells constitute a wide range of differentiation potentials (e.g., adipocytes, osteoblasts, chondrocytes, lymphocytes, erythrocytes, macrophages) as well as a complex relationship with hematopoietic and endothelial cells. Numerous studies have demonstrated that Gal-1 may be a key element in the course of hematopoietic cell differentiation (Lutomski, Fouillit *et al.*, 1997; Andersen *et al.*, 2003; Silva *et al.*, 2003; Wang *et al.*, 2004; Vas *et al.*, 2005). The K562 human leukemia cell line expresses Gal-1 in the cytosol, but upon treatment with erythropoietin these cells develop an erythroid phenotype that leads to the externalization of cytosolic Gal-1 (Lutomski, Fouillit *et al.*, 1997). Similarly, Gal-1 is externalized during adipocyte differentiation (Wang *et al.*, 2004) and is able to modulate osteoblastic differentiation (Andersen *et al.*, 2003) as well as the proliferation and death of hematopoietic stem and progenitor cells (Vas *et al.*, 2005).

Nerve structure development

Gal-1 is widely distributed in the central and peripheral nervous systems of rodents during their development. Although it has been shown that Gal-1 plays a number of important roles in the formation of the neural network of the olfactory bulb of mice (Puche *et al.*, 1996), there are no reports on its role in other regions. Gal-1 homozygous null mutant (Gal-1–/–) mice are viable and can grow into adults without any obvious phenotypical abnormalities except for a deficiency in the olfactory network (Poirier and Robertson, 1993; Tenne-Brown *et al.*, 1998) and a reduced thermal sensitivity (McGraw, Gaudet, Oschipok, Steeves *et al.*, 2005). In these mice the neuronal subpopulation in the olfactory bulb, which normally expresses Gal-1, does not reach the appropriate targets in the olfactory glomeruli (Puche *et al.*, 1996). During its development into adulthood, a rat's sensory neurons from the dorsal root ganglion express Gal-1, as do some spinal motor neurons (Regan *et al.*, 1986). The initial expression in the sensory neurons begins as they finish their final mitotic division and begin their growth toward their targets in the dorsal horn of the spinal cord. When Gal-1-expressing neurons reach their targets Gal-1 expression remains high, albeit at lower levels (Regan *et al.*, 1986; Hynes *et al.*, 1990; Sango *et al.*, 2004). In addition to neurons, Gal-1 mRNAs are also detected in the non-neuronal cells such as the pia mater, the choroid plexus, and the pineal gland as well as in reactive astrocytic and Schwann cells (Akazawa *et al.*, 2004; Sango *et al.*, 2004; Egnaczyk *et al.*, 2003).

Gal-1 and the immune system

Galectins in general, and Gal-1 in particular, are known to be deeply involved in the initiation, amplification, and resolution of inflammatory responses (Figure 4) (Almkvist and Karlsson, 2004).

T-cell homeostasis and survival

A growing body of evidence indicates that Gal-1 functions as a homeostatic agent by modulating innate and adaptative immune responses. Gal-1 induces the inhibition of cell growth and cell-cycle arrest (Blaser *et al.*, 1998; Rabinovich, Ramhorst *et al.*, 2002) and promotes the apoptosis of activated, but not resting, immune cells (Perillo *et al.*, 1995; Rabinovich *et al.*, 1998; Chung *et al.*, 2000; He and Baum, 2004). This said, resting T cells are sensitized to CD95/Fas-mediated cell death by Gal-1 (Matarrese *et al.*, 2005). Furthermore, it has been shown that the Gal-1 expressed by thymic epithelial cells promotes the apoptosis of immature cortical thymocytes *in vitro* (Perillo *et al.*, 1997), so suggesting a potential role for this protein in the processes of positive and/or negative selection within the thymic microenvironment. Gal-1 also suppresses the secretion of the pro-inflammatory cytokine interleukin-2 (IL-2) (Rabinovich, Ariel *et al.*, 1999) and favors the secretion of the anti-inflammatory cytokine IL-10 (van der Leij *et al.*, 2004) (Figure 4). All of these activities have been demonstrated by adding a relatively high concentration (μM range) of exogenous Gal-1 to T cells *in vitro*. In this context Bättig *et al.* (2004) have shown that the irreversibly dimeric form of Gal-1 is a dramatically more potent inducer of apoptosis in T cells than wild-type Gal-1. One concern regarding the proapoptotic activity of Gal-1 is whether high levels of soluble protein can be achieved *in vivo*. Recent evidence indicates that the amount of Gal-1 secreted by different cell types in the ECM is sufficient to kill T cells (Perillo *et al.*, 1995; Chung *et al.*, 2000; He and Baum, 2004). The effects of Gal-1 on immune and inflammatory cells are likely to be due to the binding and cross-linking of cell-surface glycoproteins on these cells (Galvan *et al.*, 2000) (Figure 4). As a bivalent dimer, Gal-1 binds to the glycoproteins (including CD2, CD3, CD7, CD43, and CD45) on the cell surface of T cells in a carbohydrate-dependent manner (Pace *et al.*, 1999). The regulated expression of glycosyltransferases—leading to the creation of *N*-acetyllactosamine ligands—during development and activation may determine T-cell susceptibility to Gal-1-induced cell death (Galvan *et al.*, 2000; Amano *et al.*, 2003; Carlow *et al.*, 2003). Sezary cells—the malignant T cells in cutaneous T-cell lymphomas (the Sezary syndrome or mycosis fungoides)—resist a variety of apoptosis-inducing agents including Gal-1, because of the loss of CD7 expression and altered cellular glycosylations (Rappl *et al.*, 2002; Roberts *et al.*, 2003).

Thus, a number of T-cell glycoproteins from human MOLT-4 and Jurkat T cells have been shown to be specific

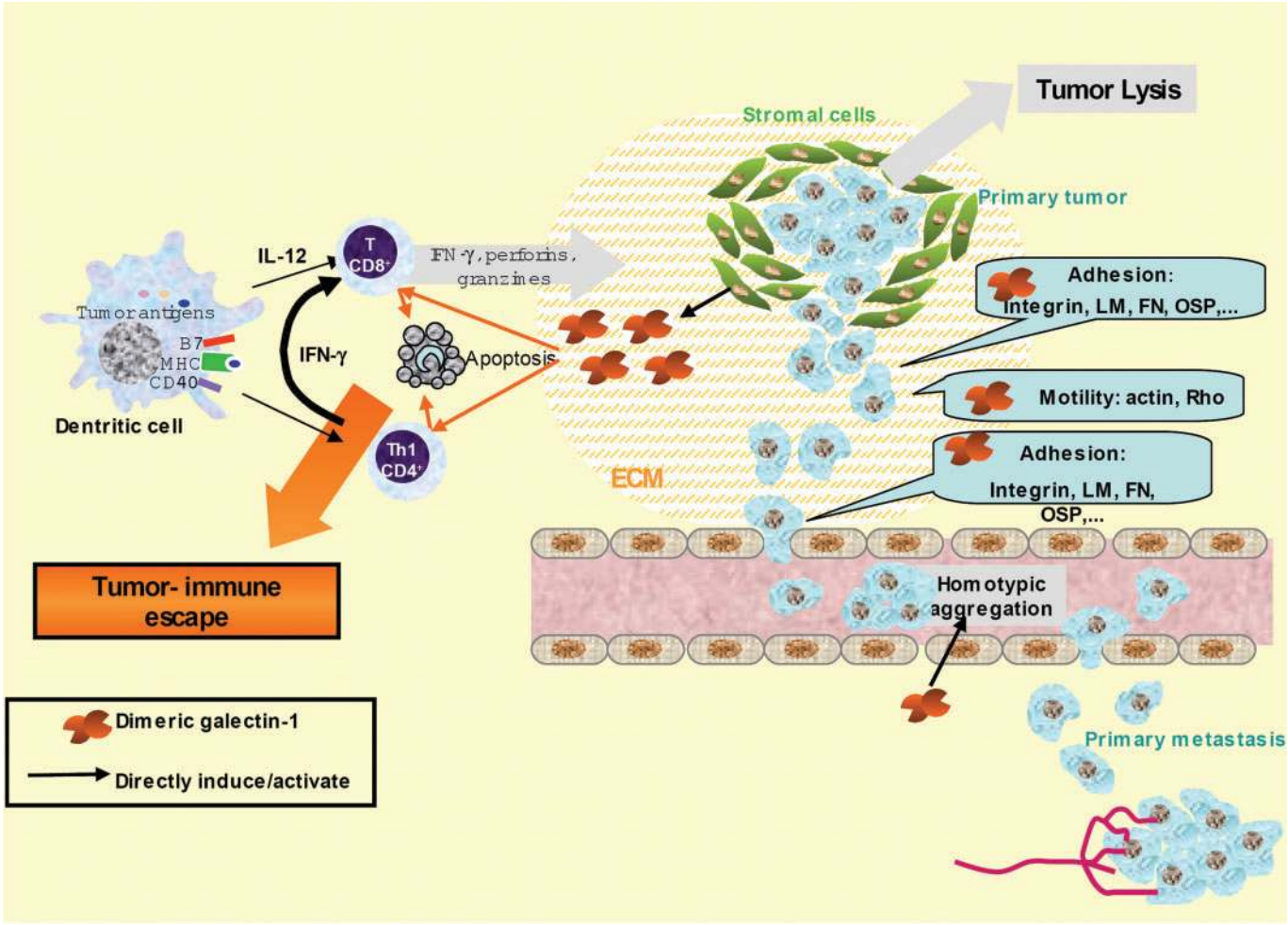

Fig. 4. Gal-1 and tumor immune privilege. The progression of the malignancy of a tumor includes the local dispersal of tumor cells into the surrounding normal tissue in addition to their long-range dispersal (metastasis). This progression is a multistep process that involves cell–cell and cell–ECM adhesion, invasion, migration, and angiogenesis. Gal-1 is involved in several of the steps of this malignant progression. Together with integrins, Gal-1 mediates tumor cell adhesion including adhesion to ECM proteins and homotypical cell adhesion. At the same time, Gal-1 can also inhibit adhesion, a phenomenon which could result in tumor cell detachment and migration. In addition, Gal-1 is involved in the mechanisms of tumor immune-escape. T cells use two main mechanisms to kill tumor cells, namely the death receptor and the granule exocytosis pathways, which involve the secretion of perforin and granzymes. Tumors can evade immune responses by secreting immunosuppressive cytokines and soluble inhibitory factors, including Gal-1. Gal-1 contributes to immune evasion by inducing apoptosis in effector T cells (Rubinstein, Alvarez *et al*., 2004; Liu and Rabinovich, 2005).

receptors for mammalian Gal-1 binding and to be involved in Gal-1-mediated T-cell death: CD45, CD43, CD7 (Pace *et al*., 1999; Walzel *et al*., 1999; Symons *et al*., 2000; Fajka-Boja *et al*., 2002). However, although the deletion mutants of the glycoproteins confirm their importance in the apoptotic response to Gal-1 (Pace *et al*., 1999, 2000; Perillo *et al*., 1995), the role of CD45 in T-cell apoptosis mediated by Gal-1 remains controversial since Gal-1 induces apoptosis in CD45-deficient T cells (Walzel *et al*., 1999; Fajka-Boja *et al*., 2002). As for CD7, it seems that only specific spliced isoforms or glycoforms of CD45 may be important in signaling Gal-1-induced cell death (Nguyen *et al*., 2001; Xu and Weiss, 2002; Amano *et al*., 2003; Lanteri *et al*., 2003).

The signal transduction events that lead to galectin-induced cell death in activated T cells involve several intracellular mediators including the induction of specific transcription factors (i.e., NFAT, AP-1), the activation of the Lck/ZAP-70/MAPK signaling pathway, the modulation of Bcl-2 protein production, the depolarization of the mitochondrial membrane potential and cytochrome *c* release, the activation of caspases and the participation of the ceramide pathway (Rabinovich, Alonso *et al*., 2000; Walzel *et al*., 2000; Hahn *et al*., 2004; Ion *et al*., 2005; Matarrese *et al*., 2005) (Figure 4). However, a recent study has shown that Gal-1-induced apoptosis in human T leukemia MOLT-4 cells deficient in Fas-induced cell death is not dependent on the activation of caspase-3 or on cytochrome *c* release—two hallmarks of apoptosis—but involves the rapid nuclear translocation of EndoG from mitochondria (Hahn *et al*., 2004), so implying that Gal-1-induced cell death might also relate to one of the other types of cell death (Broker *et al*., 2005). Furthermore, recent evidence also indicates that whereas dGal-1 can induce the exposure of phosphatidylserine (an early apoptotic marker involved in the phagocytosis of apoptotic cells) on the plasma membrane of human T leukemia MOLT-4 cells, this does not

result in cell death on activated neutrophils and on the pro-myelocytic cell line, but prepares the cells for phagocytic removal (Dias-Baruffi *et al.*, 2003). At low concentrations (the nM range) Gal-1 has been shown *in vitro* to inhibit T-cell adhesion to ECM and to modulate the tumor necrosis factor alpha (TNFα) as well as the interferon gamma (IFNγ) secretion from activated T cells (Allione *et al.*, 1998) (Figure 4). In addition, *in vivo* studies on experimental autoimmunity models have revealed the ability of Gal-1 to skew the balance toward a T2-type cytokine response by reducing the levels of IFNγ, TNFα, IL-2, and IL-12 and increasing the level of IL-5 secretion (Santucci *et al.*, 2000, 2003; Baum *et al.*, 2003) (Figure 4).

T-cell immune disorders and chronic inflammation

In vivo, Gal-1 has powerful immunoregulatory effects through its ability to inhibit T-cell effector functions (van der Leij *et al.*, 2004; Figure 4). Gal-1 treatment has resulted in improvements and even in cases of prevention in a number of experimental models of autoimmune diseases (Table III). The *in vivo* administration of Gal-1 prevents the development of chronic inflammation and impairs the ongoing disease in experimental models of autoimmune encephalomyelitis (EAE) (Offner *et al.*, 1990), arthritis (Rabinovich, Daly *et al.*, 1999), colitis (Santucci *et al.*, 2003), hepatitis (Santucci *et al.*, 2000), and chronic pancreatitis (Wang *et al.*, 2000). The ability of Gal-1 to suppress the allogenic T-cell response through apoptotic and non-apoptotic mechanisms suggests its potential use for immunosuppression in organ transplantation and graft versus host disease (GVHD) (Baum *et al.*, 2003).

Acute inflammation and allergy

In addition to its role in adaptative immune responses and chronic inflammation, Gal-1 also participates in innate immunity and acute and allergic inflammation (Liu, 2000). In phospholipase A2 (PLA2)-induced hind paw edema in rats the transmigration of both neutrophils and mast cells

Table III. Overview of animal models that have undergone Gal-1 treatment

	Human disease	Animal model	Treatment	Results	References
Inflammation-related diseases	Crohn's disease	Trinitrobenzene sulphonic acid-induced colitis in BALBc mice	rhGal-1 (1 mg/kg), prophylactic or therapeutic	Clinical and histological improvement	Santucci *et al.*, 2003
	Multiple sclerosis	Autoimmune encephalomyelitis (EAE) in Lewis rats	rhGal-1 (250 µg i.v. for 10 days, start day –3, or i.v. daily for 12 days, start day 0)	63% protection against disease (prophylactic)	Offner *et al.*, 1990
				90% no clinical signs (therapeutical)	
	Myasthenia gravis	Experimental autoimmune myasthenia gravis in New Zealand rabbits	Gal-1 (electrolectin) (prophylactic and therapeutical protocols)	Prophylactic and therapeutical effects	Levi *et al.*, 1983
	Rheumatoid arthritis	Collagen-induced arthritis in DBA/1 mice	Gene therapy: fibroblast secreting moGal-1 or daily i.p. of rhGal-1	Therapeutic effects in both protocols, skewing Th1 ≥ Th2	Rabinovich, Daly *et al.*, 1999
	Nephritis (Goodpasture's syndrome)	Nephrotoxic nephritis in Wistar Kyoto rats	rmGal-1 (1 mg/kg, every second day, 2 weeks)	Therapeutic effects	Tsuchiyama *et al.*, 2000
	T-cell mediated hepatitis	Con A-induced hepatitis in BALBc mice	rhGal-1 (i.v. at time of induction)	Prevention of liver injury	Santucci *et al.*, 2000
	GVHD	BM Tx in mice	rhGal-1 (i.p., 3×/week)	Reduced mortality	Baum *et al.*, 2003
Cancers	Human glioblastomas	Intracranial xenografts in nude mice	Transfection of anti Gal-1 antisense oligonucleotides prior to graft	Reduced mortality	Camby *et al.*, 2002
	Melanomas	Mice with subcutaneous melanoma grafts	Transfection of anti Gal-1 antisense oligonucleotides prior to graft	Reduced mortality, tumor immune-escape	Rubinstein, Alvarez *et al.*, 2004
Neuro-regeneration	ALS	H46R SOD1 transgenic mice	rGal-1/oxidized (i.m., 0.25 µg/g/week)	Delay of the onset of the disease, prolonged lifespan, and improved motor function	Chang-Hong *et al.*, 2005
	Peripheral nerve injury	Rats with surgically transected sciatic nerves	RhGal-1/oxidized (5 µg/mL by osmotic pump, 2.5 µl/h at the site of surgery)	Functional recovery	Kadoya and Horie, 2005

i.m., intramuscular injection; i.p., intraperitoneal injection; i.v., intravascular injection; moGal-1, mouse galectin-1; rhGal-1, recombinant human galectin-1.

into the tissue is reduced in the presence of Gal-1 (Rubinstein, Ilarregui *et al*., 2004), which is also responsible for the inhibition of the release of arachidonic acid from lipopolysaccharide (LPS)-stimulated macrophages, mast-cell degranulation, and eosinophil migration (Rabinovich, Sotomayor *et al*., 2000; Delbrouck *et al*., 2002; La *et al*., 2003). This suggests that signals generated by Gal-1 binding inhibit rather than promote the migration of inflammatory cells.

Gal-1 is also able to induce an oxidative burst in neutrophils that have extravasated into tissue, but not in the case of peripheral blood neutrophils (Almkvist *et al*., 2002). This enhancement of cellular activity in exudated neutrophils is referred to as the neutrophil priming that might occur through the interaction of Gal-1 with $\alpha_M\beta_2$ integrins expressed at the neutrophil cell surface (Almkvist *et al*., 2002), as has been described with respect to macrophages (Avni *et al*., 1998).

Host–pathogen (bacteria–virus–parasites) interactions

Taking recombinant Gal-1 as a basis, it has been shown that this galectin influences the ability of macrophages to control intracellular infections by inhibiting microbicidal activity, by promoting parasite replication, or by inducing host-cell apoptosis (Zuniga *et al*., 2001). While a biphasic modulation has been reported in *Trypanosoma cruzi* replication and cell viability, low concentrations (3 nM) of Gal-1 increase parasite replication and do not affect macrophage survival, higher concentrations (300 nM) are able to condemn cells to apoptosis and to inhibit parasite replication. The expression of Gal-1 is markedly upregulated after parasite or virus infection (Giordanengo *et al*., 2001; Zuniga *et al*., 2001; Lim *et al*., 2003). It has been shown on the basis of experiments using exogenously added recombinant protein that Gal-1 acts as a soluble host factor that promotes HIV-1 infectivity though the stabilization of virus attachment to host cells (Ouellet *et al*., 2005), and that the altered T-cell surface glycosylations in HIV-1 infection results in an increased susceptibility to Gal-1-induced cell death (Lanteri *et al*., 2003). In contrast, in the case of the Nipah virus infection (responsible for severe, often fatal, febrile encephalitis) of endothelial cells, dGal-1 inhibits the cell fusion of the envelope glycoproteins of the Nipah virus with the host cells and favors the secretion of proinflammatory cytokines by dendritic cells (Levroney *et al*., 2005).

Gal-1 involvement in tumor progression and tumor immune-escape

From all the studies reported in the literature and summarized in Table IV it is reasonable to assume that Gal-1 expression or overexpression in a tumor or the tissue surrounding a tumor (stroma) must be considered as a sign of the tumor's malignant progression and, consequently, of a poor prognosis for patients. This prognosis is often related to tumor immune-escape, to the long-range dissemination of tumoral cells (metastasis), or to their presence in the surrounding normal tissue, as is discussed below and illustrated in Figure 4.

Gal-1 could be involved in tumor angiogenesis because both vascular smooth muscle and endothelial cells express it (Moiseeva *et al*., 2000; Moiseeva, Williams, and Samani, 2003). Although the vessel walls of normal lymphoid tissues do not express Gal-1, the blood vessel walls of lymphomas do so in relation to their vascular density (D'Haene *et al*., 2005).

A number of mechanisms have been described that potentially contribute to tumor cell evasion from an anti-tumoral immune response (Zou, 2005). Together with the abundance of pro-apoptotic Gal-1 in privileged immune sites such as the placenta (Hirabayashi *et al*., 1989), the brain (Joubert *et al*., 1989), and the reproductive organs (Wollina *et al*., 1999) the fact that a number of studies have highlighted the expression of Gal-1 in the stromal tissue around tumors (Gillenwater *et al*., 1996; Sanjuan *et al*., 1997; Berberat *et al*., 2001; Shimonishi *et al*., 2001; van den Brule *et al*., 2001, 2003) or in the endothelial cells from capillaries infiltrating them rather than in those in the adjacent non-tumoral stroma (Clausse *et al*., 1999) suggest that Gal-1 might trigger the death of infiltrating T cells and protect these sites from the tissue damage induced by T-cell-derived proinflammatory cytokines (Figure 4). Le *et al*. (2005) have recently demonstrated a significant relation in head and neck squamous cell carcinomas (HNSCCs) between Gal-1 expression and the presence of both hypoxia markers and an inverse correlation with T-cell infiltration, a fact which suggests that hypoxia can affect malignant progression by regulating the secretion by tumor cells of proteins (like Gal-1) that modulate immune privilege. The immunomodulatory effects of Gal-1 and the correlation between Gal-1 expression in cancer cells and their aggressiveness (as described in the previous section) suggest the hypothesis that tumor cells may impair T-cell effector functions through the secretion of Gal-1, and that this mechanism may contribute toward tilting the balance in favor of an immunosuppressive environment at a tumor site (Figure 4). The blockade of the biological activity of Gal-1 in melanoma tissue results in a reduced tumor mass and stimulates the *in vivo* generation of a tumor-specific T-cell response (Rubinstein, Alvarez *et al*., 2004). These observations support the idea that Gal-1 may contribute to the immune privilege of tumors by modulating the survival or polarization of effector T cells (Figure 4).

Gal-1 in pathological nervous systems

Nerve regeneration

Gal-1 in its oxidized form—a form that lacks lectin activity—promotes neurite outgrowth (Outenreath and Jones, 1992) and enhances axonal regeneration in peripheral (Horie *et al*., 1999; Inagaki *et al*., 2000; Fukaya *et al*., 2003; Kadoya *et al*., 2005) and central (McGraw, McPhail *et al*., 2004; Rubinstein, Ilarregui *et al*., 2004; McGraw, Gaudet, Oschipok, Kadoya *et al*., 2005) nerves even at relatively low concentrations (picoM range) (Horie and Kadoya, 2000). The marked axonal regeneration-promoting activity of oxidized Gal-1 is likely to be paracrine (Figure 5). Indeed, Gal-1 is expressed in dorsal root ganglion neurons and motor neurons, with immunoreactivity restricted to the neuronal cell bodies, the axons, and the Schwann cells of adult rodents (Regan *et al*., 1986; Hynes *et al*., 1990; Horie *et al*., 1999; Fukaya *et al*., 2003) (Figure 5). After axonal

Table IV. Gal-1 expression in human tumors

Histological types	Expression in tumors as compared to normal tissues	Is Gal-1 a diagnostic marker?	Is Gal-1 a prognostic marker?	Does Gal-1 modify cell proliferation and/or cell migration?
Colon carcinomas	↑ in stroma and in epithelial tissues (Sanjuan *et al.*, 1997; Hittelet *et al.*, 2003; Nagy *et al.*, 2003)		Yes (Nagy *et al.*, 2003)	Yes (Hittelet *et al.*, 2003; Horiguchi *et al.*, 2003)
Pancreatic ductal adenocarcinomas	↑ (Grutzmann *et al.* 2004; Shen *et al.*, 2004)	Yes (Berberat *et al.*, 2001; Fitzner *et al.*, 2005)		
Intrahepatic cholangiocarcinomas	↑ in stroma and in epithelial tissues (Shimonishi *et al.*, 2001)			
Renal cell carcinomas	↑ or ↓ depending on histological grades (Francois *et al.*, 1999; Saussez *et al.*, 2005)			
Bladder transitional-cell carcinomas	↑ (Cindolo *et al.*, 1999)	Yes (Cindolo *et al.*, 1999)		
Prostate cancers	↑ in stromal tissues (van den Brule *et al.*, 2001)		Yes (van den Brule *et al.*, 2001)	
Uterine adenocarcinomas	↑ (van den Brule *et al.*, 1996)			
Choriocarcinomas	↑ (Bozic *et al.*, 2004)			
Human uterine smooth muscle tumors	No modifications (Schwarz *et al.*, 1999)			
Gliomas	↑ (Gunnersen *et al.*, 2000; Yamaoka *et al.*, 2000; Camby *et al.*, 2001, 2002; Rorive *et al.*, 2001)		Yes (Camby *et al.*, 2001, 2002)	Yes (Camby *et al.*, 2001, 2002; Rorive *et al.*, 2001)
Nonsmall-cell lung cancers	↑ (Szoke *et al.*, 2005)			Yes (Gabius *et al.*, 2002)
HNSCCs	↑ or ↓ depending on histological types (Gillenwater *et al.*, 1996; Choufani *et al.*, 1999; He *et al.*, 2004)		Yes (Le *et al.*, 2005; Saussez *et al.*, forthcoming)	

↓, decreased Gal-1 expression in tumor tissue as compared to normal tissues; –, increased Gal-1 expression in tumor tissue as compared to normal tissues.

injury, cytosolic reduced Gal-1 is likely to be externalized from growing axons and reactive Schwann cells to an extracellular space where some of the molecules may be converted into an oxidized form and may enhance axonal regeneration (Horie and Kadoya, 2000; McGraw, McPhail *et al.*, 2004; Rubinstein, Ilarregui *et al.*, 2004; Miura *et al.*, 2004; Sango *et al.*, 2004) (Figure 5). Miura *et al.* (2004) have recently identified a novel, naturally occurring, N-terminally processed form of Gal-1 that lacks the six amino-terminal residues of full length Gal-1. This isoform of Gal-1, which is monomeric under both reducing and oxidizing conditions, promotes axonal regeneration (Miura *et al.*, 2004). Since oxidized Gal-1-induced neurite outgrowth is not observed on isolated neurons (Horie *et al.*, 1999), the secreted Gal-1 probably influences the non-neuronal cells surrounding the axons, including the Schwann cells (Fukaya *et al.*, 2003), and in so doing recruits macrophages, fibroblasts, and perineuronal cells (Horie *et al.*, 2004) (Figure 5). In this respect, macrophages are potential candidates since they secrete an axonal regeneration-promoting factor when stimulated by oxidized Gal-1 (Horie *et al.*, 2004). A preclinical study using rats with surgically transected sciatic nerves has recently shown that the administration by an osmotic pump of oxidized Gal-1 at the site of surgery restores nerve function (Kadoya *et al.*, 2005).

Neural diseases

As mentioned above, Gal-1 is an endogenously expressed protein that is important in the embryonic development of primary sensory neurons and their synaptic connections in the spinal cord (Puche *et al.*, 1996; Tenne-Brown *et al.*, 1998). Various reports suggest a relation between Gal-1 expression (or altered expression) and neurological diseases. Gal-1 expression by neuronal and glial cells is closely correlated with regenerative success after injury (Wada *et al.*, 2003; McGraw, Gaudet, Oschipok, Kadoya *et al.*, 2005), and the level of autoantibodies to Gal-1 is significantly higher in patients with neurological disorders than in healthy controls (Lutomski, Joubert-Caron *et al.*, 1997). In cases of neurodegenerative amyotrophic lateral sclerosis (ALS) diseases Gal-1 accumulates in the neurofilamentous lesions (Wada *et al.*, 2003). In a recent report, Chang-Hong *et al.* (2005) show the neuroprotective effect of oxidized Gal-1 on a transgenic murine ALS model: the administration of oxidized Gal-1 to the mice delayed the onset of their

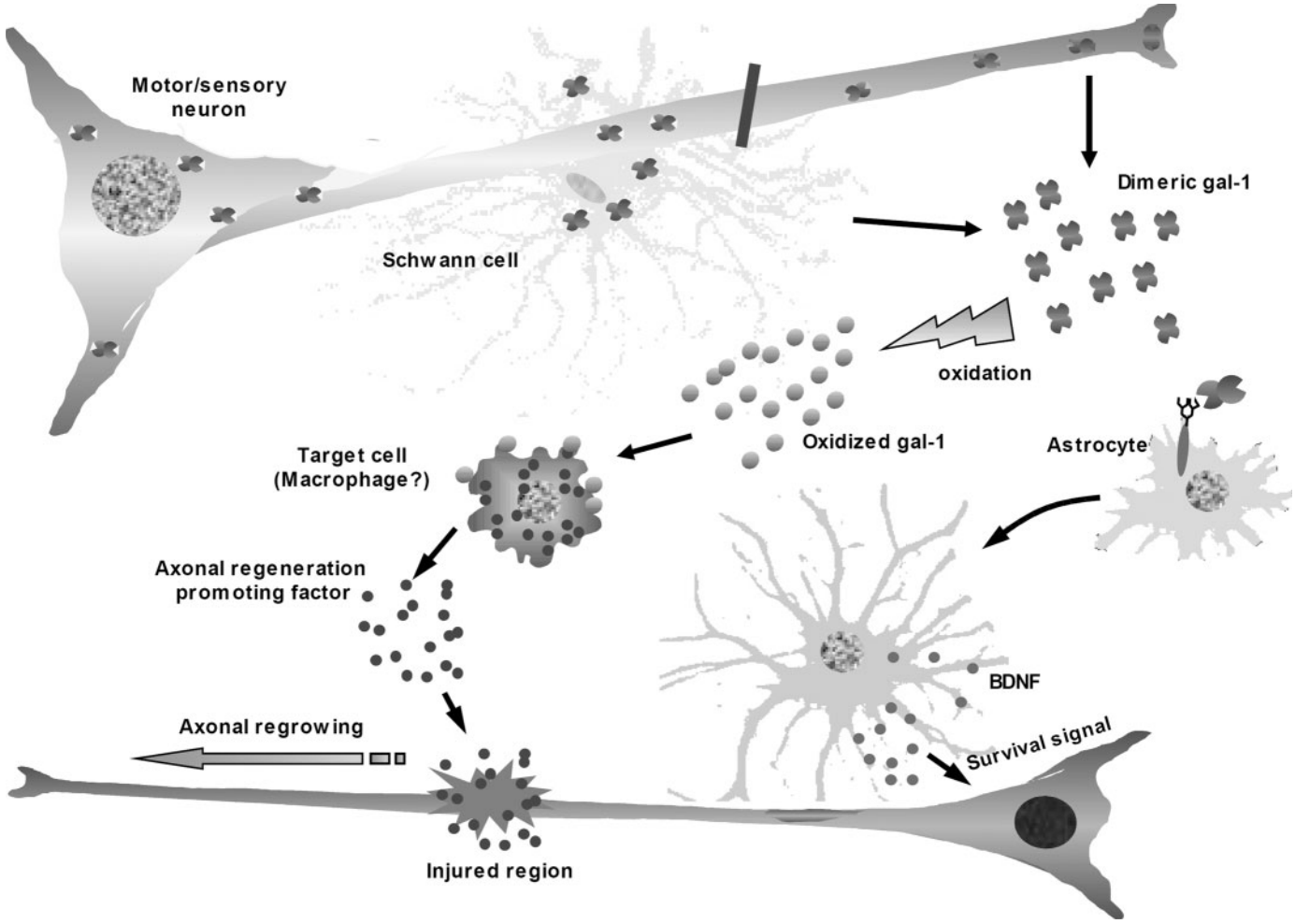

Fig. 5. Gal-1 and neuroregeneration processes. After axonal injury, cytosolic-reduced Gal-1 is externalized from growing axons and reactive Schwann cells to the extracellular space, where some of the molecules are converted into an oxidized form (Horie and Kadoya, 2000; McGraw, McPhail *et al.*, 2004; Rubinstein, Ilarregui *et al.*, 2004; Miura *et al.*, 2004; Sango *et al.*, 2004). Upon stimulation by oxidized Gal-1, macrophages secrete an axonal regeneration-promoting factor and enhance axonal regeneration (Horie *et al.*, 2004). Reduced Gal-1 induces astrocyte differentiation in a carbohydrate-dependent manner. The differentiated astrocytes then greatly enhance their production of the BDNF that, in turn, plays an important role in the survival, differentiation, and synaptic plasticity of neurons (Sasaki *et al.*, 2004).

disease, prolonged their life spans, and improved their motor functions.

In the rat brain hippocampus the expression of fosB (an early gene that directs the synthesis of the FosB and DeltaFosB proteins from the AP-1 complex of transcription factors) is induced immediately after ischemia and is accompanied by an increased expression of Gal-1, especially in neurons resistant to the injury (Kurushima *et al.*, 2005). Gal-1 induces astrocyte differentiation, with the subsequently differentiated astrocytes greatly enhancing their production of the brain-derived neurotrophic factor (BDNF) that, in turn, plays an important role in the survival, differentiation, and synaptic plasticity of neurons (Sasaki *et al.*, 2004) (Figure 5). In contrast to the effect of oxidized Gal-1 on axonal regeneration reported above, the effects of Gal-1 on astrocyte differentiation and BDNF production depend on carbohydrate-binding activity and are astrocyte-specific since no effects on neurons have been observed (Sasaki *et al.*, 2004). The Gal-1-triggered astrocyte differentiation occurs predominantly via a tyrosine dephosphorylation pathway that remains to be elucidated (Sasaki *et al.*, 2004). In this context Gal-1 may thus be considered as a means for the prevention of neuronal loss in cases of injury to the central nervous system (Egnaczyk *et al.*, 2003).

Conclusions and prospects for therapeutical applications

Gal-1 plays a number of crucial roles in (1) neuronal cell differentiation and survival in both the central and the peripheral nervous systems, and (2) the establishment and maintenance of T-cell tolerance and homeostasis *in vivo.* Furthermore, it is reasonable to state that Gal-1 expression or overexpression in tumors or the tissue surrounding them must be considered as a sign of their malignant progression, which is often related to the long-range dissemination of tumoral cells (metastasis), to their dissemination into the surrounding normal tissue, and to tumor immune-escape. Its increased expression is therefore associated with poor prognoses for large numbers of cancer patients.

Gal-1 could constitute a target for the setting up of novel treatments for a number of different diseases. The targeted overexpression (or delivery) of Gal-1 should be considered as a novel approach for the treatment of inflammation-related diseases including GVHD (Baum *et al*., 2003), arthritis (Rabinovich, Daly *et al*., 1999), colitis (Santucci *et al*., 2003), and nephritis (Tsuchiyama *et al*., 2000), for example. It could be also viewed as a potential therapeutic target in some neurodegenerative pathologies (Chang-Hong *et al*., 2005; Kadoya and Horie, 2005) and muscular dystrophies (Goldring *et al*., 2002). In the fight against cancer progression what should be developed for therapeutical applications is the targeted inhibition of Gal-1 expression. Indeed, the knock-down of the expression of Gal-1 in migrating tumor cells, or at least in gliomas (Lefranc *et al*., 2005; Camby *et al*., 2006) and melanomas (our unpublished results), could impair malignancy development in different ways, including, for example, a delay in cancer cell migration within the host tissue (as for gliomas in the brain) or at a distance (melanoma metastases), and the sensitization of migrating cancer cells to apoptosis. Indeed, migrating cancer cells are protected against apoptosis (Lefranc *et al*., 2005; Decaestecker *et al*., forthcoming). Restricting the migration of cancer cells by down-expressing the Gal-1 in them restores a certain level of sensitivity to cell death, and so to cytotoxic drugs (Lefranc *et al*., 2005; Camby *et al*., 2006; Decaestecker *et al*., forthcoming). Anti-Gal-1 compounds are thus required to combat migrating cancer cells and several groups (Andre *et al*., 2001; Nangia-Makker *et al*., 2002; Sorme *et al*., 2003), including our own (Ingrassia *et al*., 2006), are engaged in this quest. The possibility exists that such anti-Gal-1 compounds could be assayed in clinical trials (in association with cytotoxic agents) in the near future.

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Conflict of interest statement

None declared.

Abbreviations

ALS, Amyotrophic lateral sclerosis; BDNF, brain-derived neurotrophic factor; CRD, carbohydrate recognition domain; dGal-1, dimeric galectin-1; ECM, extracellular matrix; Gal-1, galectin-1; GFP, green fluorescent protein; GVHD, graft versus host disease; HNSCC, head and neck squamous cell carcinoma; IL, interleukin; RNP, ribonucleoprotein; SMN, survival of motor neuron protein.

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